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REMARKS

Claim 32 has been amended to clarify that which Applicants regard as the invention. Specifically, the phrase "in need thereof" has been replaced with "having a pathological value of plasma fibrinogen." Thus, Applicants submit that such does not raise new issues, and entry of the Amendment is proper. In addition, this amendment is supported by the specification, for example, at page 14, line 27 to page 15, line 8; and page 18, lines 6-7.

Claims 32, 38, and 39 have been amended to limit the invention to "human." This amendment is supported by the specification in Example 1, showing treatment of humans with Curcuma extract. Applicants submit that such does not raise new issues and that entry of the Amendment is proper.

Applicants have added just one new claim, claim 41, which is supported, for example, by the specification at page 18, line 6. Applicants submit that, since claim 41 further defines a pathological value of plasma fibrinogen, which Applicants assert above is not a new issue, claim 41 also does not raise new issues.

Accordingly, Applicants respectfully request entry of the Amendment.

After entry of the amendment, Claims 32-41 will be all of the claims pending in the application.

Rejection Under 35 U.S.C. § 103

At page 2 of the February 17, 2004 Office Action, claims 32-40 are rejected under 35 U.S.C. § 103(a) as being obvious over Jackson et al. (US 2002/0164374) in view of Bosca et al. (Age, 1997), Deshpande et al. (Med. Sci. Res., 1997), and Quiles et al. (BioFactors, 1998), with evidence provided by Tsuda et al. (Atherosclerosis, 1996).

Specifically, the Examiner states that Jackson teaches a pharmaceutical composition containing curcumin as an active ingredient for treating vascular diseases including atherosclerosis, and that Jackson teaches that local concentrations of fibrinogen increase as part of the chain of events leading to the formation of obstructive atherosclerotic vascular plaques and narrowing of the vessels. The Examiner states that Tsuda teaches that elevated plasma fibrinogen is known to progress to atherosclerosis (an extremely common form of arteriosclerosis) and to be one of the risk factors for the occurrence of cardiovascular disease. The Examiner further states that Bosca, Deshpande, and Quiles teach the administration of an aqueous alcoholic extract of *Curcuma longa* rhizomes to humans or to rabbits, and teach that such extracts are useful for treating and/or preventing coronary heart disease, such as arteriosclerosis.

The Examiner thus concludes that it would have been obvious to administer the curcumin-containing pharmaceutical composition taught by Jackson to a subject suffering from a cardiovascular disease, such as atherosclerosis, including atherosclerosis involving vascular plaque formation related to elevated fibrinogen levels. The Examiner contends

that the motivation to combine these teachings flows from the fact that levels of fibrinogen are a known risk factor for cardiovascular disease.

Response to Section 103 Rejection

Applicants have amended the claims to recite methods of reducing plasma fibrinogen in a "human having a pathological value of plasma fibrinogen." Applicants submit that the prior art of record does not teach or suggest that a compound present in *Curcuma* rhizomes can be effective to reduce pathological values of plasma fibrinogen in a human.

As stated previously in Applicants' Responses filed November 17, 2003 and May 12, 2004, Jackson does not teach that a curcumin-containing pharmaceutical composition can be effective to reduce fibrinogen levels, but merely that curcumin-containing pharmaceutical compositions have antioxidant, hypolipedemic, and hypercholesterolemic properties. Fibrinogen is one of many risk factorsis, and indeed is an independent risk factor for cardiovascular disease (i.e. not related to other risk factors). In addition, as discussed in said Responses, compounds which are useful for treating cardiovascular disease have unpredictable effects on fibrinogen levels. Thus, it was unexpected that administration of *Curcuma* compounds would reduce fibrinogen levels in plasma. Further, and as already illustrated by literature evidence accompanying Applicants' May 12, 2004 Response, methods of administering compounds of *Curcuma* to patients with pathological

values of fibrinogen produces superior results that were unexpected given the teachings of the prior art (i.e. reduces pathological values of plasma fibrinogen to reference values).

Accordingly, Applicants assert that claims 32-41 are not obvious, and Applicants respectfully request that this rejection be withdrawn.

With regard to pathological values of plasma fibrinogen, Applicants submit that such values were well-known in the art. Normal reference ranges for fibrinogen are about 200-400 mg/dl, as may be found in references dated prior to the present application's priority date (September 23, 1999). For example, see Statland, BE, Clinical Levels for Laboratory Tests, Second Edition [Oradell NJ; Medical Economics Books, 1987]. The reference values of Statland, which may be downloaded from http://www.westgard.com/decision.htm, are as follows (bold added):

Test	Units	Reference Interval	Decision Levels				
HEMATOLOGY RELATED TESTS			1	2	3	4	5
Antithrombin-III	% of normal	80-120	50	75			
Bleeding Time	min	2.3-9.2	10	15			
Fibrinogen in plasma	**mg/dL**	**200-400**	30	100	500		
Folate in serum	ng/mL	2-15	1.5	4.0			
Hematocrit	L/L	0.43-0.51 M	0.14	0.33	0.56	0.70	
		0.38-0.46 F					

Hemoglobin	g/dL	14-17.8 M	4.5	10.5	17	23	
		12-15.6 F					
Mean corpuscular volume	fL (cu u)	84-96	80	100			
Partial thromboplastin time	sec	30	35	45	90		
Plasminogen	%	80-120	50	75	135		
Platelet count	K/uL	150-400	10	50	100	600	1000
Prothrombin time	sec	11.5	14	16	30		
Vitamin B_{12}	pg/mL	200-900	170	250	1200		
White blood cell count	K/uL	4-11	0.5	3	12	30	

Kannel et al., *Am Heart J.* 113(4):1006-10 (1987) (attached hereto) is further evidence that pathological values of plasma fibrinogen were known in the art at the time the priority application was filed (September 23, 1999). Kannel et al. describe that the risk of cardiovascular disease is increased progressively in relation to fibrinogen values over the 180-450 mg/dl range (see page 1010, first full paragraph). Thus, based on Kannel et al., plasma fibrinogen values greater than 400 mg/dl produce a greater risk of cardiovascular disease.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue

which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Volume 113
Number 4

Fibrinogen, cigarette smoking, and risk of cardiovascular disease: Insights from the Framingham Study

William B. Kannel, M.D., Ralph B. D'Agostino, Ph.D., and Albert J. Belanger
Boston, Mass.

It is well recognized that, in addition to lipid infiltration, clotting factors, blood flow (rheology), and pliability of red blood cells are important in the evolution of atherosclerotic cardiovascular disease. Cigarette smoking has been consistently shown to be related prospectively to the occurrence of atherosclerotic diseases, including coronary disease, peripheral arterial disease, and stroke.[1] This effect has been shown to be independent of other risk factors and reversible. Fibrinogen values in the blood have also recently been shown to be an independent contributor to stroke and coronary death.[2-4] Also, fibrinogen values have been found to be higher in smokers than in nonsmokers.[2,3] This report is concerned with the net and joint effect of cigarette smoking and fibrinogen on occurrence of atherosclerotic cardiovascular disease over 12 years in the Framingham Study cohort.

METHODOLOGY

The Framingham Study has been in continuous opeation since 1948, biennially examining and following 5209 subjects for the new development of cardiovascular disease in relation to suspected predisposing factors. The sampling procedure, response rates, follow-up, clinical examination protocol, and criteria for clinical end points have been reported elsewhere.[5,6] Cigarette smoking was assessed by self-reported information on the number, brand, and filter type of cigarettes used each day.

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At the time of the tenth biennial examination, 1499 study participants had their fibrinogen values acceptably measured. There were 662 men and 837 women, who ranged in age from 47 to 79 years; of these 184 had already experienced a cardiovascular event and were ineligible for development of new first events. This left 554 men and 761 women, who were in the population at risk according to their fibrinogen values and cigarette smoking status.

Fibrinogen values were determined by the method of Swaim and Feders,[7] a modification of the Ratnoff-Menzes procedure. This involved clotting the blood by recalcification, adding thrombin, and washing the resultant clot wrapped on a glass rod which was then dried. This was then hydrolyzed by heating in sodium hydroxide and the fibrinogen value was estimated by spectrophotometry.

The net and joint effect of fibrinogen and cigarette smoking, taking other cardiovascular risk factors into account, was assessed by the Walker-Duncan multiple logistic method of analysis.[8] Subjects at risk of first cardiovascular events were followed at biennial intervals for the development of a first attack of coronary heart disease, stroke, peripheral arterial disease, or cardiac failure over the ensuing 14 years in relation to their fibrinogen and cigarette smoking status. Age-adjusted rates of cardiovascular events over 14 years were computed for each sex. Other risk factors considered in assessing the independent contribution of fibrinogen and cigarette smoking to development of cardiovascular disease included: systolic blood pressure, serum cholesterol, hematocrit, relative weight, glucose intolerance, and ECG evidence of left ventricular hypertrophy. Logistic regression analysis was used to evaluate the net effect of cigarette smoking taking fibrinogen values, along with other risk factors, into account. The net effect of fibrinogen was also similarly examined. Also, the age-adjusted incidence of

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Table I. Fibrinogen distribution in Framingham Study subjects 47 to 79 years of age*

Mean	291	mg/dL
SD	56	mg/dL
Median	288	mg/dL
Range	126-696	mg/dL

*Subjects free of cardiovascular disease at tenth examination (N = 1314).

Table II. Fibrinogen by age and sex: Framingham Study, examination 10, subjects age 47 to 79 years

	Number		*Mean (mg/dL)*	
Age	*Men*	*Women*	*Men*	*Women*
48-54	201	257	278.3	283.7
55-64	229	295	286.6	296.6
65-80	123	209	293.9	309.5

Table III. Prevalence of cigarette smoking by age and sex: Framingham Study, examination 10

	Percentage of cigarette smokers	
Age	*Men*	*Women*
48-55	48.3	49.4
55-64	40.6	38.6
65-80	25.2	16.3

cardiovascular disease was determined in each sex according to fibrinogen values in smokers and nonsmokers.

OBSERVATIONS

Fibrinogen values in the cohort ranged from 126 to 696 mg/dl with a mean of 291 and a standard deviation of 56 mg/dl (Table I). They increased about 10 mg/dl with each decade of age with values higher in women than in men at all ages (Table II). Incidence of cigarette smoking was highly prevalent and substantial at all ages, but it decreased in prevalence with advancing age and was usually greater in men than in women (Table III).

Fibrinogen and cigarettes. Age-adjusted fibrinogen values were significantly higher in cigarette smokers than in nonsmokers, and they increased with the amount smoked in each sex (Table IV). Exsmokers had values similar to nonsmokers, suggesting a direct but reversible effect (Table V). Fibrinogen was also related to other major cardiovascular risk factors in one or both sexes, more so in women than in men (Table VI). Cigarette smoking was inversely related to weight, blood pressure, and high-density lipoprotein cholesterol.

Table IV. Fibrinogen by cigarette habit: Framingham Study, subjects 47 to 79 years of age

	Mean age-adjusted (mg/dL)	
Cigarettes/day	*Men**	*Women†*
None	278	292
< 1 pack	281	296
> 1 pack	301	306

*$p < 0.001$.
†$p < 0.05$.

Table V. Age-adjusted means of fibrinogen by sex and smoking status

Smoking status	*Male (mg/dL)*	*Female (mg/dL)*
Nonsmoker	275 (N = 108)	293 (N = 371)
Former smoker	282 (N = 109)	290 (N = 115)
Current smoker*	296 (N = 336)	302 (N = 275)

*Difference significant at $p < 0.001$ for men and $p < 0.07$ for women.

Table VI. Association of cardiovascular risk factors with fibrinogen: Tenth biennial examination. Framingham Study

Cardiovascular risk factors	*Men*	*Women*
Hematocrit		*
Serum cholesterol		†
Glucose		†
Relative weight		*
Cigarettes	*	‡
Blood pressure	*	*

*$p < 0.001$; †$p < 0.01$; ‡$p < 0.05$ (blank spaces indicate $p > 0.05$).

Cardiovascular risk. Over 14 years of follow-up, 192 men and 177 women developed clinically manifest cardiovascular disease of which 202 events were coronary heart disease and 92 were strokes. The remainder were occurrences of cardiac failure and peripheral arterial disease. Age-adjusted risk in each sex increased progressively and significantly in relation to fibrinogen values (Table VII). Regression analysis indicated a diminishing impact with advancing age in women, but a similar gradient of risk in men at all ages.

Risk of coronary disease also increased progressively in relation to fibrinogen over more than a twofold range in each sex adjusted for age comparing tertiles. For coronary heart disease regression analy-

Table VII. Risk of cardiovascular disease by fibrinogen level: 14-year follow-up. Framingham Study, subjects 48 to 80 years of age

	Men			*Women*		
Fibrinogen (mg/dL)	*No. at risk*	*No. of events*	*14-year age-adjusted rate/1000**	*No. at risk*	*No. of events*	*14-year age-adjusted rate/1000†*
126-264	209	57	284	234	38	181
265-310	199	69	346	246	47	192
311-696	145	66	449	281	92	318
All	553	192	347	761	177	233

*$p = 0.0017$; †$p = 0.0004$.

Table VIII. Risk of cardiovascular disease* by cigarette smoking: 30-year follow-up. Framingham Study

	Men				*Women*			
	Age 35-64 yr		*Age 65-94 yr*		*Age 35-64 yr*		*Age 65-94 yr*	
No. of cigarettes/day	*No. of events*	*Age-adjusted rate/1000†*	*No. of events*	*Age-adjusted rate/1000†*	*No. of events*	*Age-adjusted rate/1000‡*	*No. of events*	*Age-adjusted rate/1000‡*
None	236	12	237	38	276	8	326	26
1-10	47	13	32	36	60	8	35	25
11-20	212	23	43	39	86	10	40	34
21-40	143	21	26	33	33	11	5	12
41-90	27	27	3	81	3	26	0	—
All	665	17	341	38	458	9	406	26

*Cardiovascular disease: Coronary heart disease, stroke, cardiac failure, peripheral arterial disease.
†$p < 0.001$.
‡Not significant.

sis indicated a diminishing impact with advancing age in both sexes. For stroke, risk was also related to fibrinogen, but with no indication of a waning impact with age in either sex.

In men, over the entire 30-year follow-up, cardiovascular disease in general (and coronary disease in particular) was related to cigarette smoking (Table VIII). As for fibrinogen, the risk diminished with advancing age. Unlike fibrinogen, cigarette smoking was not a significant coronary risk factor in women.

Examination of the risk of cardiovascular disease by fibrinogen level in smokers vs nonsmokers indicates an apparent effect of each in both sexes (Table IX). In either smokers or nonsmokers risk increases with increases in fibrinogen values with no indication of a stronger impact in smokers than in nonsmokers. Also, at any fibrinogen value smokers appeared at greater risk than nonsmokers. With the limited data available, fibrinogen-related disease trends were significant in smokers in men and in nonsmokers in women.

Multivariate analysis, taking all other cardiovascular risk factors into account, indicated a stronger independent contribution of fibrinogen than cigarettes to occurrence of cardiovascular disease (Table X). Each taken alone and adjusted only for age contributes significantly to occurrence of cardiovascular disease in men. However, the standardized coefficient for fibrinogen is substantially larger than that for cigarettes and is significant in both sexes.

Adding cigarettes to the bivariate model for fibrinogen only moderately reduces the size of the coefficient for fibrinogen, which remains significantly related to the occurrence of cardiovascular disease (Table X). Conversely, adding fibrinogen to the model for cigarette smoking substantially reduces the size of the coefficient so that it is no longer statistically significant in men.

COMMENTS

There are cross-sectional data which indicate that cigarette smokers have higher mean fibrinogen values than persons who do not smoke, and exsmokers

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Table IX. Risk of cardiovascular disease by fibrinogen level and smoking status: 14-year follow-up. Framingham Study, subjects 48 to 80 years of age

	14-year age-adjusted rate/1000			
	Men		*Women*	
Fibrinogen (mg/dL)	*Nonsmokers**	*Cigarette smokers†*	*Nonsmokers†*	*Cigarette smokers**
126-264	318	230	176	213
265-310	295	421	209	165
312-696	397	486	297	343

*Trend not significant.
†Trend significant at $p < 0.05$.

have lower values than continuing smokers.[1] Also, fibrinogen values are increased in proportion to the amount smoked. This suggests a direct, reversible relationship.

The effect of cigarette smoking on cardiovascular disease appears to be reversible and noncumulative, triggering lethal events in those with an already compromised coronary circulation.[9] This strongly suggests a thrombotic pathogenesis in addition to effects on platelet adhesiveness, oxygen-carrying capacity, and myocardial irritability.[9] Thus, the adverse effect of cigarette smoking on the atherosclerotic process and on the ensuing clinical events is complex. However, it is clear that its influence on thrombotic components of the process is most important.

There is increasing evidence that acute thrombotic occlusion plays a major role in the occurrence of a myocardial infarction and sudden death.[10] Cigarette smoking is most closely linked to these clinical events and only weakly, if at all, related to the occurrence of angina pectoris.[9] Also, there is no good evidence to indicate that risk of clinical atherosclerotic events is related to the duration of the exposure to cigarettes. Rather, it is related to the current number of cigarettes smoked each day.[9] Furthermore, there is consistent evidence that within 1 year of quitting the habit risk drops to half that of those who continue to smoke and approximates that of those who have never smoked.[9,10]

Estimates to date suggest that 25% to 50% of the relation of cigarette smoking to occurrence of atherosclerotic cardiovascular disease is attributable to the effect of smoking on fibrinogen levels, which in turn enhances thrombotic tendencies leading to occlusive clinical events.

The findings reported herein do not stand alone. There are now three other prospective studies which have shown the association between fibrinogen and occurrence of coronary heart disease.[2-4] The Goteborg study also showed a relationship between fibrinogen and stroke fatality rates.[3] There is also ample evidence from other sources that cigarette smoking is related to the occurrence of all major thrombotic, atherosclerotic diseases, including coronary disease, stroke, and peripheral arterial disease.[1,9,10]

There are few means for directly lowering fibrinogen values. However, it is apparent from its relationship with cardiovascular risk factors, that there is a potential for reducing fibrinogen and risk of cardiovascular disease by the recommended measures of reduction of cholesterol, weight control, lowering of blood pressure and, above all, quitting cigarette smoking. We thus have further insight into the

Table X. Logistic regression analysis of impact of cigarette smoking and fibrinogen values on cardiovascular disease: 14-year follow-up. Framingham Study, subjects age 48 to 80 years

	Standardized regression coefficients	
	Men	*Women*
Fibrinogen		
Univariate	0.359‡	0.330‡
Bivariate*	0.336‡	0.268§
Smoking		
Univariate	0.134 (NS)	0.031 (NS)
Bivariate*	0.197‖	0.179 (NS)
Fibrinogen and smoking jointly		
Fibrinogen†	0.314‡	0.259§
Smoking†	0.153 (NS)	0.163 (NS)

NS = not significant.
*Age and other variable.
†Bivariate with other variable.
‡$p < 0.001$.
§$p < 0.01$.
‖$p < 0.05$.

pathogenesis of cigarette-induced atherosclerotic cardiovascular disease and further reasons to prohibit cigarette smoking.

SUMMARY

During the tenth biennial examination, 1315 Framingham study participants free of cardiovascular disease had fibrinogen measured along with other major cardiovascular risk factors including cigarette smoking. The fibrinogen values were significantly higher in smokers than in nonsmokers, increased with the amount smoked in each sex, and exsmokers had values as low as those of nonsmokers. Over 10 years of follow-up, 165 men and 147 women developed cardiovascular disease, the risk in both sexes increasing progressively in relation to antecedent fibrinogen values over the 180 to 450 mg/dl range. Risk gradients for cardiovascular disease in men diminished with advancing age.

In men, risk of cardiovascular disease was related to cigarette smoking. This was true in the multivariate case taking all standard risk factors into account. As for fibrinogen, the impact diminished with advancing age. Regression coefficients were actually larger in the multivariate than in the univariate case because of a negative correlation between smoking and blood pressure. Fibrinogen contributed to cardiovascular disease, risk taking into account both cigarette smoking and other risk factors. When fibrinogen is added to the multivariate model for prediction of cardiovascular disease the coefficient for smoking becomes much reduced and is no longer statistically significant. However, each independently contributed to risk in cross-sectional analysis. These data provide another mechanism whereby cigarette smoking influences the occurrence of atherocardiovascular disease and also another reason for prohibiting cigarette use.

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